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# Enantioselective Nitrile Anion Cyclization to Substituted Pyrrolidines. A Highly Efficient Synthesis of (3*S*,4*R*)-N-*tert*-Butyl-4-Arylpyrrolidine-3-Carboxylic Acid

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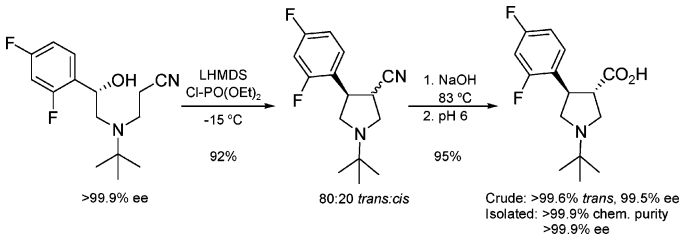
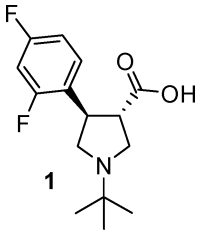



A practical asymmetric synthesis of N-*tert*-butyl disubstituted pyrrolidines via a nitrile anion cyclization strategy is described. The five-step chromatography-free synthesis of (3*S*,4*R*)-1-*tert*-butyl-4-(2,4-difluorophenyl)pyrrolidine-3-carboxylic acid (**2**) from 2-chloro-1-(2,4-difluorophenyl)-ethanone achieved a 71% overall yield. The cyclization substrate was prepared via a catalytic CBS asymmetric reduction, *t*-butylamine displacement of the chlorohydrin, and a conjugate addition of the hindered secondary amine to acrylonitrile. The key nitrile anion 5-exo-tet cyclization concomitantly formed the pyrrolidine ring with clean inversion of the C-4 center to afford 1,3,4-trisubstituted chiral pyrrolidine in >95% yield and 94−99% ee. Diethyl chlorophosphate and lithium hexamethyldisilazide were shown to be the respective optimum activating group and base in this cyclization. The *trans-cis* mixture of the pyrrolidine nitrile undergoes a kinetically controlled epimerization/ saponification to afford the pure *trans*-pyrrolidine carboxylic acid target compound in >99.9% chemical and optical purity. This chemistry was also shown to be applicable to both electronically neutral and rich substituted phenyl substrates.

## Introduction

Substituted pyrrolidines are ubiquitous among natural products and compounds of pharmacological interest.[1] Their biological and pharmacological importances have inspired the development of numerous synthetic methods to provide such substrates on a practical scale and, especially, in enantiomerically pure form. In conjunction with a recent drug development program, we required a practical synthesis of *trans*-trisubstituted pyrrolidine **1** suitable for multi-kilogram preparation.[2] Herein, we report a highly efficient asymmetric route to **1** via a novel nitrile anion cyclization strategy. This route has been demonstrated to be general for the preparation of other pyrrolidine analogues.




Compound **1** is a trisubstituted pyrrolidine, with *tert*-butyl moiety on nitrogen, carboxylic acid on C3, and difluorophenyl on C4 in trans 3*S*,4*R* configuration. In

(1) (a) Yus, M.; Foubelo, F. *J. Org. Chem.* **2001**, *66*, 6207−6208. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781−1813. (d) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, *6*, 633−640. (e) Laschat, S. *Liebigs Ann.* **1997**, *1*, 1−11. (f) Dewick, P. M. *Medicinal Natural Products*; J. Wiley & Sons: Chichester, U.K., 1997; Chapter 6. (g) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964 and references therein. (h) Wang, C. J. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 583−621. (i) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379−423. (j) Hill, K. R. *Chem. Alkaloids* **1970**, 385−429.

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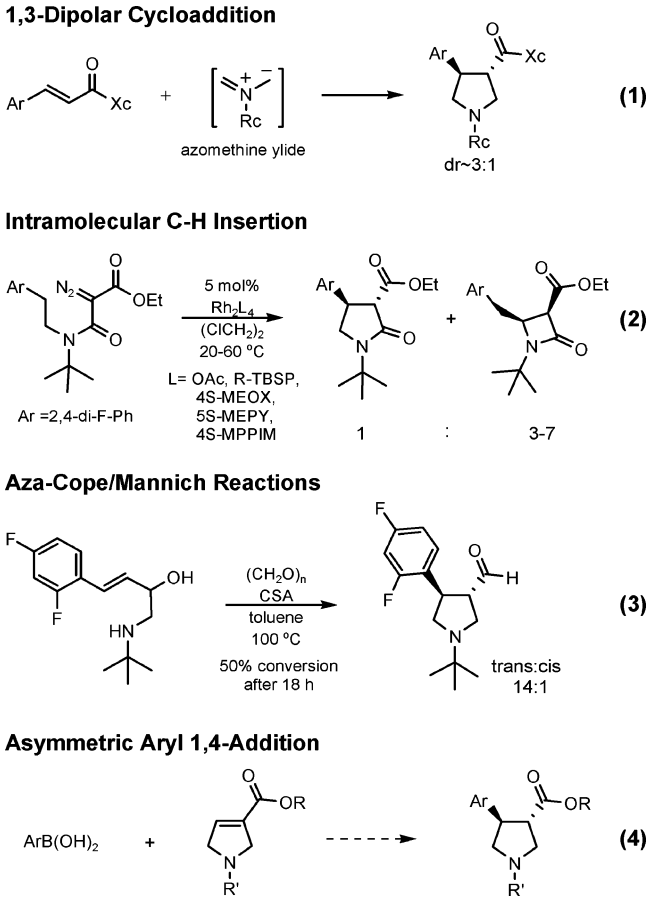
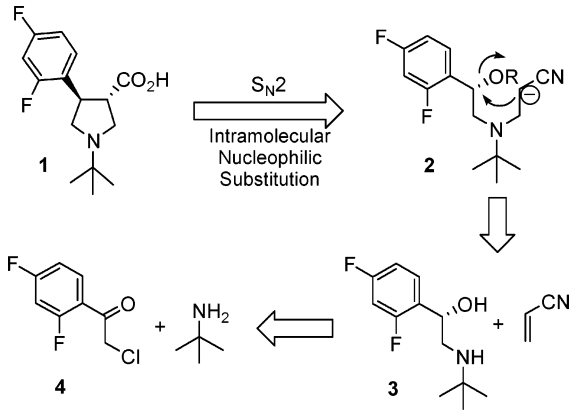
**SCHEME 1. Approaches to Trisustituted Pyrrolidine 1**




designing a synthesis, we made the following considerations: (1) since direct installation of *tert*-butyl group on to pyrrolidine nitrogen is not a trivial reaction, we would install the *tert*-butylamine as a single entity; (2) the trans configuration of the two adjacent stereogenic centers in which the C3 center bearing the carboxylate group being epimerizable could simplify the synthesis to a one chiral center problem. This later consideration was derived from the observation that pure trans ester when treated with NaOH/MeOH, gave initially a 97:3 trans/cis mixture of the esters, and then proceeded to give only trans acid.

While a number of routes to asymmetric *trans*-3,4-disubstituted pyrrolidines have been reported, none is generally efficient or effective. Several potential routes to **1** were explored based on literature precedents (Scheme 1). A [3+2] dipolar cycloaddition approach[3] using chiral auxiliaries has been studied extensively, most recently by Karlsson et al.[4] The studies from our laboratory were consistent with literature findings, with a moderate diastereoselectivity of 3−4:1 at best obtained even when double chiral auxiliaries were used (eq 1).[5] Other approaches, such as intramolecular C−H insertion[6] as shown in eq 2, gave mainly the four-membered ring product instead of the five-membered lactam. Application of Overman's aza-Cope/Mannich strategy[7] afforded some success; however, we were unable to drive the reaction to more than 50% conversion and more forcing conditions led to decomposition (eq 3). Utilization of Miyaura−Hayashi's chiral rhodium complexes to catalyze 1,4-addition of aryl boronic acid[8] to the tetrahydropyrrole esters gave the desired product in good ee with bulky esters, but poor conversion. Better yields were obtained with smaller esters; however, the enantioselectivity was significantly lower (eq 4).[5] Furthermore, access to the α, β-unsaturated pyrrolidine ester was not straightforward.

**SCHEME 2. Retrosynthetic Analysis of Pyrrolidine Acid 1**




Further retrosynthetic analysis of **1** led to the synthetic strategy outlined in Scheme 2, where the molecule was dissected along the bond bearing the two stereogenic centers to give acyclic alcohol nitrile **2**. We envisaged nitrile **2** deriving from a conjugate addition of amino alcohol **3** to acrylonitrile, and **3** from the corresponding ketone **4** via an asymmetric reduction. The key step would be the nitrile anion intramolecular $S_N2$ displacement of the benzylic leaving group in **2** to concomitantly form the five-membered ring and the C4 stereocenter. The steric effect of the *tert*-butyl group should facilitate the cyclization reaction. Nitrile anions are well-known powerful nucleophiles and have been extensively studied in cyclization reactions, but applications to heterocyclic compounds are less extensive.[9] Achini[10] describes a nitrile anion cyclization strategy to substituted pyrrolidines via

(2) Ujjainwalla, Feroze; Chu, Lin; Goulet, Mark T.; Lee, Bonnie; Warner, Daniel; Wyvratt, Matthew J. International Patent WO 0268388, 2002.

(3) Ma, Z.; Wang, S.; Cooper, C. S.; Fung, A. K. L.; Lynch, J. K.; Plagge, F.; Chu, D. T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 883−887.

(4) (a) Karlsson, S.; Han, F.; Hogberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2605−2616. (b) Karlsson, S.; Hogberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1977−1982.

(5) Belyk, K. M.; Beguin, C. D.; Palucki, M.; Grinberg, N.; DaSilva, J.; Askin, D.; Yasuda, N. *Tetrahedron Lett.* **2004**, *45*, 3265−3268.

(6) (a) Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775−1777. (b) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79−82. (c) Wee, A. G. H.; Liu, B.; McLeod, D. D. *J. Org. Chem.* **1998**, *63*, 4218−4227.

(7) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622−6629.

(8) (a) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052−5058. (b) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852−6856. (c) For a Review, see: Hayashi, T. *Synlett* **2001**, 879−887. (d) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951−5955. (e) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047−4056.

(9) For a review see: (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1−23. (b) Fleming, F. F.; Funk, L. A.; Altundas, R.; Sharief, V. *J. Org. Chem.* **2002**, *67*, 9414−9416. (c) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885−2888. (d) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Org. Lett.* **2002**, *4*, 2493−2495. (e) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297−302. (f) Achini, R.; Oppolzer, W. *Tetrahedron Lett.* **1975**, *16*, 369−372.

(10) Achini, R. *Helv. Chim. Acta* **1981**, *64*, 2203−2218.

displacement of a benzylic chloride; however, the question of enantioselectivity was not addressed. Because of the potential to form a benzylic cation and participation by the adjacent amino group, a nonracemic version of this strategy poses the question of chiral fidelity.[11] Would there be any chiral leakage due to the $S_N1$ pathway or the aziridium formation? Would the cyclization proceed with clean inversion or retention? The answer to these questions and the successful development of this strategy are outlined below.

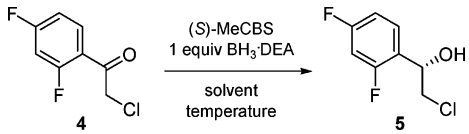
## Results and Discussion

**Asymmetric Reduction of Chloro-ketone 4.** 2-Chloro-1-(2,4-difluorophenyl)ethanone (**4**) was identified as a cost-effective[12] starting material toward the synthesis of amino-alcohol **3**. Many options were considered for this asymmetric reduction. The asymmetric transfer hydrogenation[13] of **4** using 0.2% of [cymene]RuCl[R,R-TsDPEN] in MeOH/ $HCO_2H/Et_3N$ gave **5** in 86% ee and >95% yield. Replacing the aryl ligand with a bulkier hexamethylbenzene in the same catalyst and increasing the loading to 2% gave **5** in 91% ee. Jiang[14] has reported the reduction of ketone **4** using sodium borohydride/TMSCl catalyzed by (*S*)-α,α-diphenylpyrrolidine methanol at 25 °C in 93% yield and 92% ee. Aryl chloromethyl-ketones have also been asymmetrically reduced using catalytic (*S*)-MeCBS, and Burkhardt describes the advantages of using borane-diethylaniline as the borane source.[15a] In addition, adding ketone to the reducing agents at 31−32 °C improves the enantioselectivity.[15] Building on this literature precedent, we determined that the controlled addition of ketone **4** to the reducing complex at 40 °C afforded alcohol **5** in >98% ee's, and allowed the (*S*)-MeCBS catalyst loading to be reduced to as low as 0.1 mol % from the typical 5−10 mol % used in these reductions (Table 1).

Because it was observed that product **5** tends to co-distill with toluene during in vacuo solvent removal, the reaction solvent was switched to MTBE. Using 0.5 mol % (*S*)-MeCBS, ketone **4** was reduced with 1 equiv of borane-diethylaniline complex in MTBE at 40 °C, with the controlled addition of the ketone over a 10 h period. Alcohol **5** was isolated in 98% yield and 98.9% ee as the *S*-enantiomer on multikilogram scale.

***tert*-Butylamine Displacement.** Conversion of crude chloro-alcohol **5** to amino-alcohol **3** was accomplished by dissolving **5** in a methanol/*tert*-butylamine mixture and heating to reflux (56−60 °C) in the presence of 1.0 equiv of solid NaOH. The formation of both regioisomeric amino-alcohols **3** and **7** suggested the displacement of the chloride proceeded via formation of the epoxide **6** followed by ring opening, and in fact the epoxide can be observed by HPLC analysis. The epoxide was isolated and its structure confirmed by NMR and LC/MS. The presence of methanol accelerates both the ring closure and epoxide opening (Scheme 3). With 1:1 MeOH/*tert*-butylamine, the displacement produced an 80:20 ratio of amino alcohols **3**:7. Decreasing the amount of methanol led to reduced levels of the undesired regioisomer, with only 4% **7** being formed with a 1:5 ratio of MeOH/ *tert*-butylamine. After workup of the latter conditions, crystallization from heptane afforded an 89.8% isolated yield of amine **3** (from ketone **4**), that was 99.9% pure by LC area% at 210 nm with >99.9% ee as the (*S*)-enantiomer. This crystallization rejected all of isomer **7** and increased the enantiomeric purity of isolated amine **3** (98.9% ee in the reaction mixture).

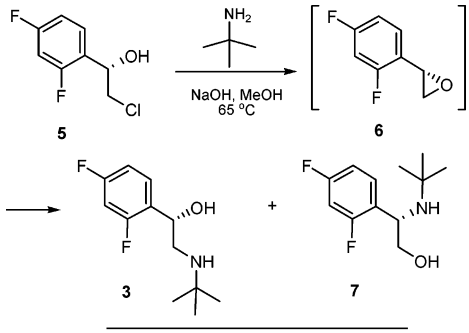
**TABLE 1. (*S*)-MeCBS-Catalyzed Reduction of 4**




| solvent | catalyst mol % | temp. | add'n time of **4** | optical purity of **5**[a] |
|---|---|---|---|---|
| toluene | 10 | −20 °C | 2.5 h | 83.8% ee[b,c] |
| − | 10 | +27 °C | 4 h | 98.2% ee |
| − | 1 | +36 °C | 6.5 h | 97.6% ee |
| MTBE | 1 | − | 5 h | 98.6% ee |
| − | 0.5 | − | 1.3 h | 95.4% ee |
| − | 0.5 | − | 1.3 h | 93.7% ee[c] |
| − | 0.5 | +40 °C | 10 h | 98.9% ee |
| − | 0.1 | − | 8 h | 94.2% ee |

[a] Determined by chiral HPLC analysis. [b] $BH_3$·$SMe_2$. [c] 0.67 eq borane.

**SCHEME 3. Conversion to Amino-Alcohol 3**




| MeOH : *t*BuNH$_2$ | 3 : 7 |
|---|---|
| 1 : 1 | 80 : 20 |
| 1 : 5 | 96 : 4 |

**Acrylonitrile Conjugate Addition.** Initial experiments on the conjugate addition of amino-alcohol **3** to acrylonitrile found the reactions were sluggish and gave incomplete addition due to the steric hindrance of the amine and retro-Michael reaction. Employing excess acrylonitrile in acetic acid−methanol mixtures at reflux[10] for 20 h typically gave a 75% assay yield and 65% isolated yield. Unreacted starting material was readily removed by an aqueous acetic acid wash and crude **8** could be crystallized from heptane in excellent chemical and optical purities. In an effort to improve the yield, further investigation revealed that the acetic acid actually prevented further conversion (75:25 equilibrium mixture).

(11) Intramolecular nitrile anion $S_N2$ reaction α to a trifluoromethyl group: (a) Katagiri, T.; Irie, M.; Uneyama, K. *Tetrahedron: Asymmetry* **1999**, *10*, 2583−2589. (b) Katagiri, T.; Yamaji, S.; Handa, M.; Irie, M.; Uneyama, K. *Chem. Commun.* **2001**, 2054−2055.

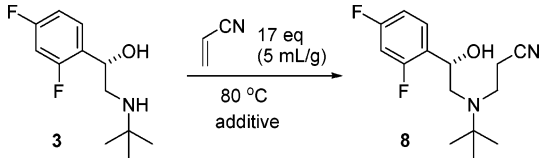
(12) 2-Chloro-2′,4′-di-fluoro-acetophenone (**5**) is available from Bayer at $30/kg on metric tone scale. (*S*)-MeCBS is available from Callery at $50/10 g on 500 kg scale. 0.5 mol % catalyst equates to 10 g catalyst per kg of **5**.

(13) Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373−4376 and references therein.

(14) Jiang, B.; Feng, Y.; Zheng, J. *Tetrahedron Lett.* **2000**, *41*, 10281−10283.

(15) (a) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1523−1526, and references within. (b) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2003**, *68*, 10146−10151.

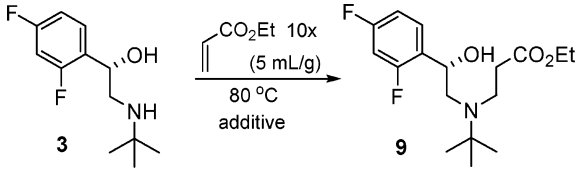
**TABLE 2. Effect of Additives in the Conjugate Addition of 3 to Acrylonitrile**




| | additive | | | 24 h | | 48 h | |
|---|---|---|---|---|---|---|---|
| entry | EtOH (5 eq) | HCONH 2 (5 eq) | mont. K10 (10 wt %) | LCAP[a] conversion 8/ (3+8) | 8% yield | LCAP conversion 8/(3+8) | 8% yield |
| 1 | | | | 90.6 | 83.7 | 95.8 | 92.9 |
| 2 | + | | | 92.8 | 88.7 | 94.8 | 88.7 |
| 3 | | + | | **97.3** | **92.1** | **97.2** | **90.4** |
| **4** | + | + | | **96.6** | **93.7** | **96.4** | **97.1** |
| 5 | + | | + | 91.6 | 86.2 | 93.9 | 88.7 |
| 6 | | + | + | 97.2 | 87.0 | 90.0[b] | 70.3[b] |
| 7 | + | + | + | 96.4 | 90.4 | 96.4 | 95.4 |

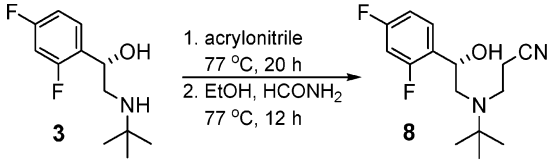
[a] HPLC area% at 210 m. [b] Uncertained data due to solvent evaporation.

**SCHEME 4. Conjugate Addition of 3 to Ethyl Acrylate**




w/out additives: 62% (24 h); 80% (48 h)
w/ additives: 72-78% (24 h); 61-85% (48 h)

**SCHEME 5. Optimized Conjugate Addition of Amino-alcohol 3 to Acrylonitrile**

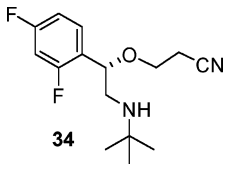



98% assay yield
92% isolated yield
chem. purity >99.6 %
optical purity >99.9%

Refluxing in neat acrylonitrile without acetic acid gave an improved 85−90% conversion after 24 h, but the remaining 10−15% was slow to convert. Various additives and physical activation methods were explored in hopes of driving the reaction to completion.[16] After screening a number of additives, we focused on three. As shown in Table 2, both ethanol and formamide[17] exhibited positive effects, whereas acidic clay Montmorillonite K10[18] was not beneficial. Ultimately, the inclusion of one equivalent each of ethanol and formamide, introduced at the latter stages of the reaction cleanly drove the reaction to completion. The strong hydrogen-bond donor formamide provided activation toward conjugate addition on the acrylonitrile, while ethanol minimized impurity formation. Conjugate addition of **3** to ethyl acrylate was also screened under the same conditions, and in all cases the yields were improved with the additives but were 15−20% lower relative to reactions with acrylonitrile (Scheme 4).

Thus, heating a mixture of amino-alcohol **3** and acrylonitrile at 77 °C for 20 h, followed by addition of one equivalent each of formamide and ethanol and continued heating for another 12 h, afforded nitrile **8** in 98% assay yield. After crystallization from heptane, nitrile **8** was isolated in 92% yield with 99.9 LC area% purity and >99.9% ee (Scheme 5). The structure of **8** was also confirmed by single-crystal X-ray analysis.

Interestingly, when the reagents above were reacted in the presence of a catalytic amount $CsCO_3$, the *O*-alkylation product, 3-[(1*S*)-2-(*tert*-butylamino)-1-(2,4-difluorophenyl)ethoxy]propanenitrile (**34**), was produced in >85% isolated yield.



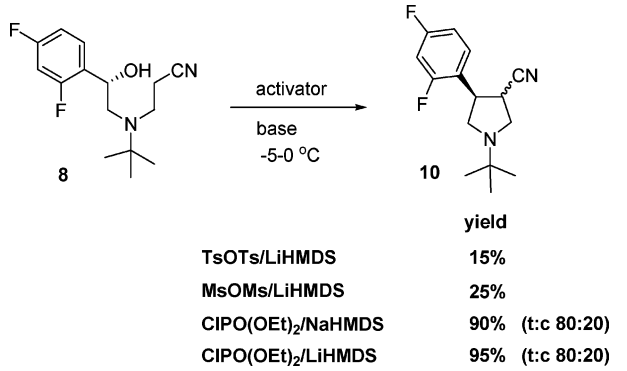

**Nitrile Anion Cyclization.** Initial attempts for the cyclization of **8** using $Ts_2O$ or $Ms_2O$ and Li-hexamethyldisilazide (Li−HMDS) (2 equiv) gave only 15% and 25% of desired pyrrolidine nitrile **10**, respectively, under various mixing modes and temperatures. The reactions produced many byproducts with large amounts of starting material remaining. Importantly, hydrolysis of the mixture gave the corresponding acid in >99% ee, indicating no racemization occurred upon cyclization. To address this problem, we explored less reactive activators. Diethyl chlorophosphate emerged as an excellent choice,[19] which, with the use of 2 equiv of Na−HMDS, produced desired pyrrolidine nitrile **10** in >90% yield as an 80:20 trans/cis mixture (Scheme 6). The yield and the purity of pyrrolidine nitrile **10** were affected by the amount of HMDS base and the nature of the counterion used in the cyclization step. Treatment of nitrile **8** with 2.35 equiv

(16) (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052−9055. (b) Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975−976. (c) Jenner, G. *Tetrahedron* **1996**, *52*, 13557−13568. (d) Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827−830.

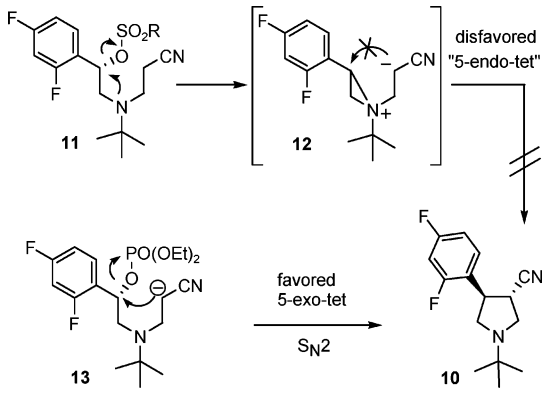
(17) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510−514.

(18) Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045−9048.

**SCHEME 6. Effect of Activator in the Cyclization**




**SCHEME 7. Proposed Mechanisms**




Na−HMDS and 1.1 equiv diethyl chlorophosphate afforded cyclized nitrile **10** in 91% assay yield.

A possible explanation for these observations may be that mesylate, being a better leaving group, was displaced by the adjacent basic nitrogen to form aziridium **12** (Scheme 7). Nitrile anion cyclization of **12** requires a disfavored 5-endo-tet geometry, and other competitive pathways ensued. Upon workup, aziridium **12** is hydrolyzed by water in an $S_N2$ fashion to regenerate starting material **8**. On the other hand, phosphate **13** is not activated enough to form the aziridium ion, but is sufficiently activated to be displaced in a $S_N2$ manner by nitrile anion in a favorable 5-exo-tet geometry.

Under the above protocol, as much as 4% of dimeric nitrile **14** was also formed, which was converted to nitrile acid **15** in the subsequent hydrolysis step. The corresponding trimer and tetramers were also detected by LC/MS. It is known that nucleophilic aromatic substitution of aryl fluorides by secondary nitrile anions is significantly affected by the counterion when hexamethyldisilazide base is used.[20] The reactivity trend was $K^+ > Na^+ > Li^+$, with the lithium base producing almost no fluoride displacement. When 2.15 equiv Li−HMDS was used in the cyclization reaction, pyrrolidine nitrile **10** was

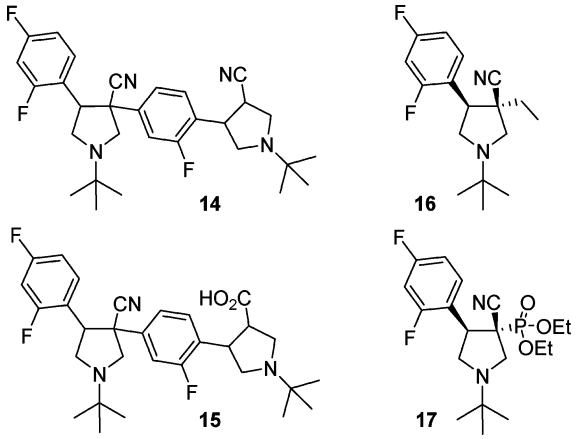



**FIGURE 1.** Impurities from the cyclization step.

obtained in 95% assayed yield with <0.5% of bis-nitrile **14**. Subsequent saponification followed by pH adjustment and crystallization afforded 99.5 LCAP pure pyrrolidine acid **1** with no detectable amounts of **15**. Another low level impurity present in the crystallization liquors was alpha-ethylated pyrrolidine nitrile **16** (identified by NMR, LC-MS and independent synthesis), indicating that diethyl phosphate was acting as an ethylating agent.

The order of reagent addition in the nitrile anion cyclization also affected the yield and the quality of the product. Charging 1.05 equiv of diethyl chlorophosphate to the alcohol-nitrile **8** followed by the addition of 2.1 equiv of Li−HMDS produced better yields of pyrrolidine **10** (95% vs 90%) and better purity (98 vs 95 LCAP) than the sequential addition of 1.0 equiv of LiHMDS, followed by 1.05 equiv of chlorophosphate, then 1.1 equiv LiHMDS. The crude cyclized nitrile obtained from the former method also gave higher wt % purity (95% vs 83%), which allowed us to use less NaOH in the next step.

The optimized procedure involved addition of 2.1 equiv of Li−HMDS to a solution of alcohol nitrile **8** and 1.05 equiv of diethyl chlorophosphate in THF at −15 °C, followed by aging for 2 h at this temperature. After aqueous quench, the assay yield of pyrrolidine nitrile **10** in the organic phase was ∼97% as an 80:20 trans:cis mixture. The major impurity at 2−3% was *trans*-diethyl phosphate pyrrolidinonitrile **17**, based on NMR and LC/MS, which was confirmed by independent synthesis from pyrrolidine nitrile **10** with Li−HMDS and diethyl chlorophosphate.

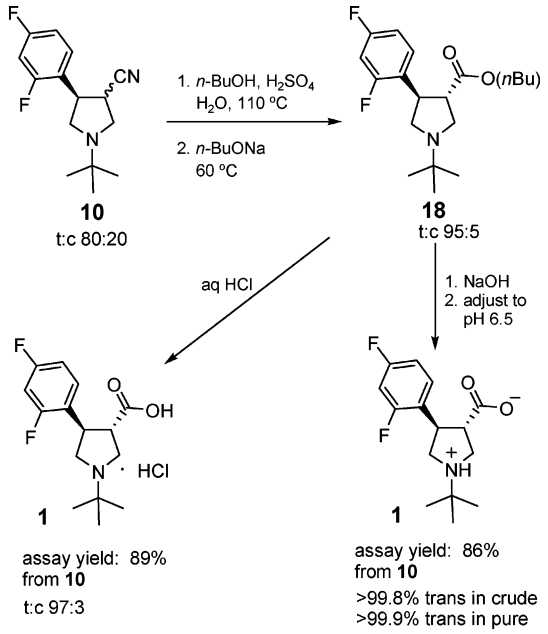
After the aqueous quench, despite the aqueous layer having a pH of 11−12, the organic phase still contained large amounts of diethyl phosphate (by $^{31}P$ NMR) and hexamethyldisilazane byproducts. These impurities were easily removed by further acid−base extractions. The assay yield of the desired product after the extractions was 92% and was nearly free of diethyl phosphoric acid and silicon-containing species.

The level of impurity **17** remained unchanged at ∼3% throughout the workup. Interestingly, a purified sample of this impurity was shown to be completely consumed under the subsequent hydrolysis condition to produce mainly the desired pyrrolidine acid **1** along with small amounts of α-ethylated pyrrolidine **16**, which was resistant to hydrolysis. The latter minor impurity was completely rejected in the crystallization of **1**.

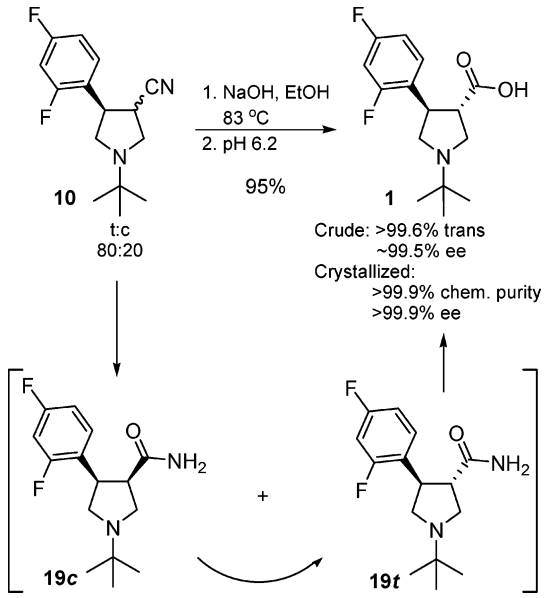
(19) (a) Song, Z. J.; Zhao, M.; Frey, L.; Li, J.; Tan, L.; Chen, C. Y.; Tschaen, D. M.; Tillyer, R.; Grabowski, E. J. J.; Volante, R.; Reider, P. J.; Kato, Y.; Okada, S.; Nemoto, T.; Sato, H.; Akao, A.; Mase, T. *Org. Lett.* **2001**, *3*, 3357−3360. (b) Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E. *J. Org. Chem.* **1999**, *64*, 9658−9667. (c) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886−888.

(20) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712−713.

**SCHEME 8. Hydrolysis/Epimerization of 10 via Ester 18**



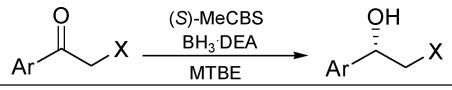

**SCHEME 9. One-step Conversion of *trans-cis* Mixture Pyrrolidine Nitrile 10 to *trans*-Pyrrolidine Acid 1**

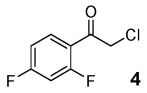
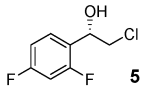
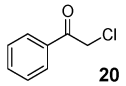
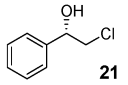
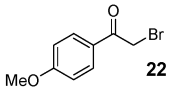
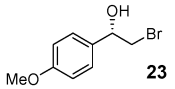



The ester anion cyclization of substrate **9** under the above conditions afforded the corresponding pyrrolidine esters in yields which were generally 15−20% lower than the nitrile analogues.

**Epimerization/Saponification of 10.** Initially, the 80:20 trans:cis mixture of pyrrolidine nitrile **10** was converted to a mixture of *n*-butyl esters under sulfuric acid catalysis, followed by epimerization with *n*-BuONa, and then hydrolysis to the acid (Scheme 8). The best trans:cis ratio of *n*-butyl esters achieved was 95:5. Hydrolysis of esters with HCl afforded the HCl salt of **1** in 89% overall yield, which led to a minor upgrade the trans:cis ratio (97:3). On the other hand, hydrolysis of the *n*-butyl ester by NaOH and subsequent pH adjustment to 6.5 afforded pyrrolidine acid **1** in 86% yield and >99.9 chemical and optical purities.

**TABLE 3. (*S*)-MeCBS Catalyzed Asymmetric Reduction**




| Ketone | Alcohol | % ee |
|---|---|---|
|  **4** |  **5** | 98.9% |
|  **20** |  **21** | 99.8% |
|  **22** |  **23** | 91%[a] |

[a] Substrate added as a THF solution instead of MTBE.

The basic hydrolysis of nitrile **10** with aq NaOH in ethanol was examined, which proceeded through intermediate amides **19**, and reached 98% conversion to acid **1** within 4 h with <1% of amides remaining. Both *cis*- and *trans*-amides were observed by LC/MS during reaction and the structure of *trans*-amide **19*t*** was confirmed by LC/MS and independent synthesis (by treatment of *trans*-pyrrolidine acid with CDI and ammonium hydroxide). It is reasonable to postulate that the hydrolysis of both *cis*-nitrile **10** and *cis*-amide **19*c*** to the corresponding *cis*-acids are slow relative to epimerization, which provided a mechanism for complete conversion of *cis*-nitrile **10** to *trans*-acid **1**.

This procedure produced crude pyrrolidine acid **1** in >99.6% trans with an optical purity of 99.5% ee, indicating that there was practically no chirality leakage in the cyclization-hydrolysis-epimerization process. **1** was isolated by crystallization from IPA/MTBE in 95% yield with 99.97 LCAP purity and >99.9% ee on multi-kg scale. Thus, an efficient direct one-step basic epimerization/hydrolysis of the pyrrolidine nitrile mixture to the *trans*-pyrrolidine acid **1** was achieved.[21]

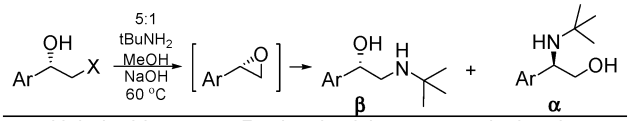
**Expansion of Scope.** To probe the generality of the nitrile anion cyclization strategy, we studied the electronic effect of the aryl moiety. Since benzylic leaving groups can be easily ionized to produce the benzylic cation, the chiral integrity can be lost due to an $S_N1$ pathway, especially with electronic-rich aryl moieties. The phenyl and 4-methoxyphenyl analogues were prepared to test the viability of the nitrile cyclization chemistry with more demanding substrates.

In the (*S*)-MeCBS catalyzed asymmetric reduction (Table 3), chloroacetophenone gave the chlorohydrin in excellent e.e. (99.8%).[22] Bromo 4-methoxy acetophenone[22] gave a slightly lower e.e. (91%) of the bromohydrin due to the need for THF to solublize the substrate for delivery

(21) (a) Aoyagi, Y.; Jain, R. P.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3472−3477. (b) Rabinovitch, B. S.; Winkler, C. A. *Can. J. Res.* **1942**, *20B*, 185−188.

(22) (a) Kawanami, Y.; Murao, S.; Ohga, T.; Kobayashi, N. *Tetrahedron* **2003**, *59*, 8411−8414, and references therein. (b) Hong, Yaping; Gao, Yun; Nie, Xiaoyi; Zepp, Charles M. *Tetrahedron Lett.* **1994** *35*, 6631−4.

**TABLE 4. Regioselectivity of *Tert*-Butylamine Addition**



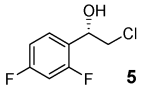
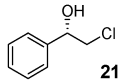
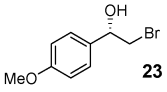
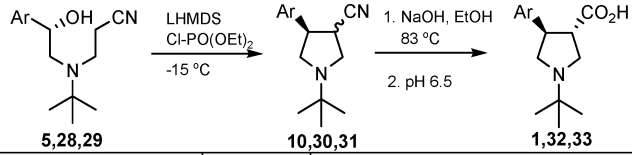
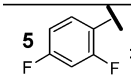
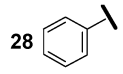
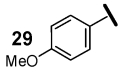

| Halo-hydrin 5,21,23 | Regioselectivity β: α | Isolated Yield (ee) of β |
|---|---|---|
|  5 | 96:04 (**3**:**7**) | 92% (>99.9% ee) (**7**) |
|  21 | 90:10 (**24**:**25**) | 80% (>99.5% ee) (**24**) |
|  23 | 85:15 (**26**:**27**) | 80% (99% ee) (**26**) |

**TABLE 5. Nitrile Anion Cyclization and Epimerization/Hydrolysis**




5,28,29 10,30,31 1,32,33

| 5,28,29 | | 10,30,31 | 1,32,33 | | | |
|---|---|---|---|---|---|---|
| Ar | ee | trans/ cis | assay yield | crude ee | isolated yield | ee |
| **5**  | >99.9% | **10** 80:20 | **1** 98% | 99.5% | 95% | >99.9% |
| **28**  | 99% | **30** 95:05 | **32** 96% | 94% | 85%[a] | 99% |
| **29**  | 99% | **31** 90:10 | **33** 98% | 95% | 62%[a] | >99% |

[a] Unoptimized.

into the reaction mixture. In the *tert*-butylamine displacement step, interestingly, the electronic effect prominently affected the regiochemistry. As shown in Table 4, the *tert*-butylamine displacement gave increased attack at the benzylic position as the electron donating ability increased. In the cyclization and saponification steps (Table 5), using diethyl chlorophosphate as the activator, both substrates **28** and **29** gave near quantitative yields of pyrrolidine acids **32** and **33** with ≤3% chiral erosion. Recrystallization provided enantiomerically pure materials in both cases.

In summary, we have demonstrated a highly efficient nitrile anion cyclization strategy for the asymmetric synthesis of N-*tert*-butyl disubstituted pyrrolidine acids. Diethyl phosphate was shown to be the optimum benzylic leaving group in the key displacement-cyclization reaction that proceeded with clean inversion of the asymmetric center. Lithium counterion of bis(trimethylsily)-amide base is preferred over the sodium for minimizing impurity formation. Another key feature of the synthesis is the kinetic control hydrolysis/epimerization of *cis*-pyrrolidine nitrile via the *cis*-pyrrolidine amides which epimerized faster relative to hydrolysis and funneled all *cis*-nitrile to *trans*-pyrrolidine acid. We have also shown that simple additives such as formamide accelerated the conjugate addition of hindered amine to acrylonitrile. The five-step chromatography-free synthesis of the optically pure trisubstituted pyrrolidine acid **1** was achieved in 71% overall yield from readily available starting materials on multi-kg scale. This chemistry was also shown to be applicable to both electronically neutral and rich substituted phenyl substrates.

## Experimental Section

**(S)-2-Chloro-1-(2,4-difluorophenyl)ethanol (5).** To a solution of (*S*)-2-methyl-CBS-OAB (131 mL of 1.0 M solution in toluene), borane-*N*,*N*-diethylaniline (4.26 kg, 26.1 mol) in MTBE (10 L) heated to 40 °C, was added a solution of 2-chloro-1-(2,4-difluorophenyl)ethanone (5042 g, 26.46 mol) in MTBE (16 L) over 10 h. The homogeneous solution was stirred at 40 °C for 1 h, then allowed to cool to 18 °C and stirred overnight. The reaction could be assayed for complete consumption of ketone using HPLC Condition A: $t_R$ for ketone **4**, 14.91 min, alcohol **5**, 13.31 min, toluene, 16.78 min, diethylaniline, 3.00 min, Me-OAB, 5.93 min. Methanol (2.3 L) was added over 60 min, maintaining the temperature at <20 °C with cooling (warning: $H_2$ evolution and MTBE vapors). The homogeneous solution was stirred 30 min; then 2.5 N aq HCl (31.5 L) was added over 30 min and the temperature maintained at 22−25 °C with cooling. After stirring 30 min, the phases were separated. The organic phase was washed with saturated aqueous NaCl, then concentrated in vacuo to obtain 5040 g of chloro-alcohol **5** for a 99% yield (an oil at 25 °C, solidified at 5 °C). The chiral assay (HPLC Condition D) of chloro-alcohol **5** gave a 99.45:0.55 ratio of S:R enantiomers (98.9% ee). bp 69−71 °C at 15 mmHg; $^1$H NMR ($CDCl_3$) $\delta$ 7.51 (m, 1H), 6.91 (m, 1H), 6.80 (m, 1H), 5.16 (dd, $J$ = 8.2, 3.2 Hz, 1H), 3.79 (dd, $J$ = 11.2, 3.4, 1H), 3.62 (dd, $J$ = 11.2, 8.2, 1H), 3.02 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.7 (dd, $J$ = 249.6, 12.0), 159.7 (dd, $J$ = 248.5, 11.7), 128.6 (dd, $J$ = 9.7, 5.7), 123.0 (dd, $J$ = 13.5, 3.8), 111.6 (dd, $J$ = 21.2, 3.7), 103.8 (t, $J$ = 25.4), 67.8 (d, 2.1), 49.4; HRMS *m/z* calcd for $C_8H_7OClF_2$ + $Cl^-$, 226.9847, found 226.9842.

**(1*S*)-2-(*tert*-Butylamino)-1-(2,4-di-fluorophenyl)ethanol (3).** The above concentrated MTBE solution of **5** (5040 g, 26.2 mol) was diluted with methanol (5 L); then *tert*-butylamine (25 L) was added. The mixture warmed on mixing to 45 °C. The mixture was cooled to 25 °C, and solid NaOH pellets (1048 g) were added. No exotherm was observed, and the mixture was stirred and warmed to reflux. During this time the nature of the suspended solids changed to a thin slurry. The reaction was monitored using HPLC Condition A: $t_R$ for chloro-alcohol **5**, 13.31 min, epoxide, 14.71 min, amino-alcohol **4**, 4.45 min, regiomeric amino-alcohol, 3.78 min. After 2 h, if chloro-alcohol remains, additional NaOH can be added. After 12−20 h at reflux, the mixture is concentrated in vacuo to 1/3 volume; then water (5 L) and MTBE (20 L) are added. The phases are separated and the aqueous phase is re-extracted with MTBE (2 × 2 L). The combined extracts are washed with sat aq NaCl (1 L) and then concentrated in vacuo. Heptane (40 L) is added, and concentration is continued to bring the volume to 20 L. The mixture is heated to ∼90 °C to dissolve solids then allowed to cool to 22 °C to crystallize. The mixture is cooled to 0 °C, stirred 12−15 h, and then filtered. The filtrate is washed with cold heptane (2 × 5 L), then dried in vacuo at 35 °C to obtain 5.35 kg of crystalline amino-alcohol in 89% isolated yield. The chiral assay (HPLC Condition D) gave a >99.95:<0.05 ratio of S:R enantiomers (>99.9% ee). mp (DSC): onset 115.35 °C, end 118.66 °C, peak 117.22 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.52 (m, 1H), 6.88 (m, 1H), 6.76 (m, 1H), 4.85 (dd, $J$ = 8.6, 3.4, 1H), 2.94 (m, 1H), 2.52 (m, 1H), 1.10 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.1 (dd, $J$ = 247.4, 12.0), 159.7 (dd, $J$ = 247.9, 12.0), 128.3 (dd, $J$ = 13.6, 3.8), 111.1 (dd, $J$ = 20.9, 3.5),

103.4 (t, $J$ = 32.0), 66.0, 50.4, 48.7, 29.1 (3C). Anal. Calcd for $C_{12}H_{17}F_2NO$: C, 62.87; H, 7.47; F, 16.57; N, 6.11. Found: C, 62.93; H, 7.67; F, 16.24; N, 6.13.

An analytical sample of epoxide **6** was prepared from chloroalcohol using NaOH/MeOH: bp 89−91 °C at 30 mmHg; $^1$H NMR ($CDCl_3$) $\delta$ 7.14 (m, 1H), 6.77−6.87 (m, 2H), 4.08 (m, 1H), 3.14 (dd, $J$ = 5.5, 4.1, 1H), 2.75 (dd, $J$ = 5.4, 2.5); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.51 (dd, $J$ = 249.1, 12.0 Hz), 161.55 (dd, $J$ = 249.6, 12.0 Hz), 126.9 (dd, $J$ = 9.7, 5.5 Hz), 121.0 (dd, $J$ = 13.4, 3.8 Hz), 111.5 (dd, $J$ = 21.2, 3.5 Hz), 103.7 (t, $J$ = 31.9 Hz), 50.2, 46.6 (d, $J$ = 5.5 Hz).

An analytical sample of regioisomer **7**, (2*R*)-2-(*tert*-butylamino)-2-(2,4-difluorophenyl)ethanol, was purified by silica gel chromatography and its hydrochloride salt was prepared: mp (DSC): onset 185.89 °C, end 192.80 °C, peak 190.77 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.47 (bs, 1H), 8.87 (bs, 1H), 8.37 (m, 1H), 7.02 (m, 1H), 6.83 (m, 1H), 5.7 (bs, 1H), 4.79 (m, 1H), 4.28 (dd, $J$ = 13.1, 8.9, 1H), 3.71 (dd, $J$ = 13.1, 2.8, 1H), 1.44 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 163.4 (dd, $J$ = 252.9, 12.3), 159.6 (dd, $J$ = 249.8, 11.9), 131.4 (dd, $J$ = 9.7, 3.1), 117.5 (dd, $J$ = 12.7, 4.0), 112.7 (dd, $J$ = 21.2, 3.5), 104.3 (t, $J$ = 26.0), 64.0, 60.0, 54.2, 27.0 (3C). Anal. Calcd for $C_{12}H_{17}F_2NO.HCl$: C, 54.24; H, 6.83; F, 14.30; N, 6.02; Cl, 13.34. Found: C, 54.37; H, 6.91; F, 14.06; N, 5.39; Cl, 13.41.

**3-{*tert*-Butyl[(2*S*)-2-(2,4-difluorophenyl)-2-hydroxyethyl]amino}propanenitrile (8).** A mixture of aminoethanol **3** (5.205 kg, 22.68 mol) and acrylonitrile (26.9 L, 408.24 mol) was heated at reflux (~77 °C) under nitrogen atmosphere. The reaction was monitored by HPLC Condition B: $t_R$ for amino-alcohol **3**, 4.5 min; alcohol-nitrile **8**, 12.8 min; acrylonitrile, 6.70 min. After heating for 22 h (~90% conversion), 1 equiv each of ethanol (1.32 L, 22.68 mol) and formamide (0.9 L, 22.68 mol) was added, and heating continued for 15 h. After cooling to 22 °C, the solution was concentrated by distillation at 80−90 Torr and 20−22 °C. After reaching 12 L volume (about 22 L distillate collected), the residue was diluted with isopropyl acetate (22 L) and concentrated at 55−75 Torr and 22−27 °C. This was repeated, and then diluted with 24 L isopropyl acetate to give a total volume of ~34 L. Acrylonitrile content relative to isopropyl acetate was determined to be <2.4 vol % by GC analysis. Gummy polymer was allowed to settle, and the supernatant was filtered (10−15 um porosity). The filter cake was washed with isopropyl acetate and the filtrate was diluted with a total of 24 L isopropyl acetate. The combined filtered organic (~54 L) was washed with a solution made up of acetic acid (52 mL, 4 mol %), saturated aqueous NaCl (3.1 L) and water (31.2 L). This is followed by washing with 12% aqueous NaCl (2 × 34 L). The resulting organic was assayed to contain 6.36 kg (99.3%) of **8**.

The organic solution was concentrated at 15−45 Torr and 5−29 °C and flushed with a total of 30 L heptane, during which time the product crystallized. The slurry was diluted with 13 L heptane to give a total volume of 23 L (<0.2% IPAC, <50 ppm $H_2O$). The mixture was stirred at 0−5 °C for 1 day and then filtered, and washed with 5 °C heptane (14 L). The wet cake was vacuum-dried at 22 °C under nitrogen to afford 5.89 kg (92%) of **8** as a crystalline white solid (purity: 99.9 LCAP). The loss to mother liquor and washes were 13 g (0.2%). The chiral assay (HPLC Condition D) of isolated **8** was 100 area% the desired S enantiomers (100% ee). The mother liquor/wash, gave a 97.3:2.7 ratio of S:R enantiomers. mp (DSC): onset 60.20 °C, end 64.15 °C, peak 62.61 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.55 (m, 1H), 6.90 (m, 1H), 6.77 (m, 1H), 4.84 (dd, $J$ = 10.2, 3.1, 1H), 3.66 (bs, −OH), 3.00−2.83 (om, 3H), 2.62−2.47 (om, 2H), 2.45 (dd, $J$ = 13.9, 10.3, 1H), 1.15 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.1 (dd, $J$ = 247.7, 11.9), 159.6 (dd, $J$ = 247.5, 11.9), 128.0 (dd, $J$ = 9.5, 6.5), 125.1 (dd, $J$ = 13.7, 3.6), 118.6, 111.4 (dd, $J$ = 20.9, 3.3), 103.4 (t, $J$ = 25.6), 65.4, 57.9, 55.7, 47.3, 27.2 (3C), 20.2; $^{19}$F NMR ($CDCl_3$) $\delta$ −112.25 (d, $J$ = 6.9), −116.27 (d, 6.8). Anal. Calcd for $C_{15}H_{20}F_2N_2O$: C, 63.81; H, 7.14; N, 9.92; F, 13.46. Found: C, 63.79; H, 7.30; N, 9.93; F, 13.31.

**Ethyl *N*-(*tert*-Butyl)-*N*-[(2*S*)-2-(2,4-difluorophenyl)-2-hydroxyethyl]-$\beta$-alaninate (9).** A mixture of aminoethanol **3** (2.0 g, 8.7 mmol) and ethyl acrylate (47.7 mL, 436.2 mmol) was heated at 80 °C for 3 days and at 60 °C for 2 days under nitrogen atmosphere. The reaction was monitored by HPLC Condition B: $t_R$ for amino-alcohol **3**, 4.5 min; alcohol-ester **9**, 14.7 min; ethyl acrylate, 7.3 min. At the end of the above reaction time, the ratio of **3**:**9** was 5.5:94.5. The reaction mixture was diluted with toluene (60 mL) and washed with an aqueous acetic acid solution (30 mL $H_2O$ and 0.15 mL acetic acid), $H_2O$ (10 mL), and then saturated $NaHCO_3$ solution (15 mL). The organic was dried over $Na_2SO_4$ and concentrated to dryness to afford 2.44 g oil of **9** (85%) with an HPLC purity of 98% at 210 nm. $^1$H NMR ($CDCl_3$) $\delta$ 7.57 (dd, $J$ = 15.2, 8.3, 1H), 6.89 (m, 1H), 6.76 (m, 1H), 4.85 (dd, $J$ = 10.3, 3.4, 1H), 4.25 (bs, −OH), 4.18 (m, 2H), 2.94 (m, 2H), 2.87 (dd, $J$ = 13.5, 2.8, 1H), 2.63−2.45 (m, 2H), 2.38 (dd, $J$ = 13.8, 10.4, 1H), 1.30 (t, $J$ = 7.1, 3H), 1.13 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 172.6, 162.1 (dd, $J$ = 247.3, 12.0), 159.8 (dd, $J$ = 247.3, 12.0), 128.2 (dd, $J$ = 9.1, 7.0), 125.8 (dd, $J$ = 14.1, 3.6), 111.36 (dd, $J$ = 21.0, 3.0), 103.4 (t, $J$ = 15.1), 65.2, 60.6, 57.9, 55.6, 47.3, 36.5, 27.3, 14.3.

**(4*R*)-1-*tert*-Butyl-4-(2,4-difluorophenyl)pyrrolidine-3-carbonitrile (10).** To a solution of alcohol nitrile **8** (5.73 kg, 99.9%, 20.28 mol) in dry THF (31.3 L) at −20 °C was added chloro diethyl phosphate (3.79 kg, 21.29 mol). 1.35 M Li−HMDS in THF solution (31.5 L, 42.58 mol) was slowly added over 1.5 h at −15 ± 3 °C. The reaction was monitored by HPLC Condition B: $t_R$ for amino-alcohol, 4.50 min; *cis*-pyrrolidine nitrile, 12.14 min; *trans*-pyrrolidine nitrile, 12.71 min; nitrile-alcohol, 12.80 min. After aging at these temperatures for 2 h and with HPLC assay confirming complete conversion to **10** (as a 80:20 trans:cis mixture), the mixture was quenched with water (50.6 L) at <15 °C. The resulting mixture was extracted with *n*-heptane (40.5 L) at 20 °C. The organic layer was washed with 10% NaCl solution (52 L). The organic layer (90 L, 58.3 mg/mL) has ~5.2 kg product **10** as a 80:20 trans:cis mixture (97%). The organic layer was carefully extracted with 3 N HCl solution (40.6 L, 121.8 mol) at <35 °C (exothermic). The aqueous layer (58 L) was adjusted to pH 11−12 with 50% NaOH (6.13 L, 116.1 mol), and extracted with *n*-heptane (54 L). During pH adjustment, significant ammonia gas was released. The organic phase was washed once with 10% NaCl solution (26 L). Pyrrolidine nitrile **10** (as a 80:20 trans:cis mixture) in heptane solution (48 kg total) was assayed by HPLC to be 4.93 kg (92% yield; >92 LC area%) and was used as is in the next step.

Analytically pure *trans*- and *cis*-pyrrolidine nitrile were obtained by prep HPLC and crystallized as the hydrochloride salt. **(3*R*,4*R*)-1-*tert*-Butyl-4-(2,4-difluorophenyl)pyrrolidine-3-carbonitrile hydrochloride (*cis*-10 HCl).** mp (DSC): onset 257.91 °C, end 263.37 °C, peak 262.15 °C; $^1$H NMR ($CD_3OD$) $\delta$ 7.57 (m, 1H), 7.16−7.03 (om, 2H), 4.82 (s, OH), 4.20−4.08 (m, 2H), 4.07−3.90 (m, 3H), 3.89−3.76 (m, 1H), 1.53 (s, 9H); $^{13}$C NMR ($CD_3OD$) $\delta$ 165.0 (dd, $J$ = 193.3, 12.5), 162.5 (dd, $J$ = 192.9, 12.5), 131.5, 118.9 (dd, $J$ = 14.3, 3.7), 118.3, 113.0 (dd, $J$ = 21.7, 3.5), 105.4 (t, $J$ = 26.2), 64.2, 51.8, 51.1, 40.2, 35.0, 24.9 (3C); $^{19}$F NMR ($CD_3OD$) $\delta$ −111.29, −112.61 (d, $J$ = 6.8). Anal. Calcd for $C_{15}H_{19}ClF_2N_2$: C, 59.90; H, 6.37; N, 9.31; F, 12.63; Cl, 11.79. Found: C, 59.76; H, 6.26; N, 9.40; F, 12.54; Cl, 11.43. **(3*S*,4*R*)-1-*tert*-Butyl-4-(2,4-difluorophenyl)pyrrolidine-3-carbonitrile Hydrochloride (*trans*-10 HCl).** mp (DSC): onset 179.23 °C, end 182.83 °C, peak 181.85 °C; $^1$HNMR ($D_2O$) $\delta$ 7.42 (m, 1H), 7.03−6.96 (om, 2H), 4.06−3.79 (om, 5H), 3.46 (bt, $J$ = 11.6, 1H), 1.38 (s, 9H); $^{13}$C NMR ($D_2O$) $\delta$ 163.2 (dd, $J$ = 180.9, 12.6), 160.8 (dd, $J$ = 180.8, 12.7), 130.2 (dd, $J$ = 10.2, 5.4), 116.9, 116.8, 112.1 (dd, $J$ = 21.7, 3.4), 104.6 (t, $J$ = 26.0), 63.2, 51.1, 49.3, 41.4, 32.3, 23.7 (3C); $^{19}$F NMR ($D_2O$) $\delta$ −109.87 (d, $J$ = 7.7), −112.87 (d, $J$ = 8.5); HRMS *m/z* [M + H]$^+$ calcd for $C_{15}H_{19}F_2N_2$, 265.1516; found, 265.1517.

**(3S,4*R*)-1-*tert*-Butyl-4-(2,4-difluorophenyl)pyrrolidine-3-carboxylic Acid (1).** A solution of crude pyrrolidine nitrile

**10** (4.88 kg, 18.46 mol) in heptane (~65 L total) from the previous step was solvent-switched to an ethanolic solution (~20.6 L total). To the solution was added 50% NaOH (2.7 L, 51.15 mol) over 2 min with stirring. The mixture, which exothermed from 16 to 34 °C, was heated to reflux at 78−80 °C under nitrogen for 5 h (or until product >95 A%). The reaction was monitored by HPLC Condition C: $t_R$ for trans-pyrrolidine amide, 10.48 min; cis-pyrrolidine acid, 11.26 min; cis-pyrrolidine amide, 11.81 min; trans-pyrrolidine acid, 12.80 min; trans- & cis-pyrrolidine nitrile, 13.05 min; alpha ethylated pyrrolidine nitrile, 18.10 min; C-phosphate pyrrolidine nitrile, 18.91 min. Both starting material and the intermediate amides were <0.8 A% at end of 5 h reflux. Significant ammonia gas was released during the reaction. After cooling to 20 °C, the solution was diluted with ethanol (25.4 L) and methanol (40.6 L) to give a total volume of ~88 L. The solution was cooled to 12 °C then adjusted to apparent pH 6.5 with 96% $H_2SO_4$ (1.42 L, 51.15 mol), while maintaining the temperature at ~20 °C. The resulting slurry was filtered through a bed of Solka-floc (5 kg) and anhydrous powder $Na_2SO_4$ (4 kg), and washed with 1:1 EtOH:MeOH (20 L). The filtrate was re-filtered (5 $\mu$m filter), concentrated and solvent-switched to a 2-propanol solution (~15 L). The product crystallized during solvent switch, and the batch was then heated to reflux at ~80 °C for 2 h which only partially dissolved product. After cooling to 16 °C, MTBE (30.4 L, 3 vol relative to IPA) was slowly added to the mixture over 5 h. After stirring at 16−17 °C for 3 days, the slurry was filtered and washed with 12 L 1:3 IPA:MTBE. After vacuum (150 Torr) drying at 50 °C afforded 5.09 kg of **5** as a white crystalline solid. The yield was 95% for the step (87% overall for the 2-step). Product loss to the ML/washes were 160 g (3%). **1**: purity, 99.97 LCAP (Condition B), >99.99% ee (Condition E). mp (DSC): onset 215 °C, peak 217 °C; $^1$H NMR ($D_2O$) $\delta$ 7.30 (m, 1H), 6.92−6.85 (om, 2H), 4.68 (OH), 3.75−3.66 (om, 3H), 3.45 (bm, 1H), 3.30−3.14 (om, 2H), 1.32 (s, 9H); $^{13}$C NMR ($D_2O$) $\delta$ 176.5, 162.8 (dd, $J$ = 123.7, 12.6), 160.3 (dd, $J$ = 124.5, 12.7), 129.9 (dd, $J$ = 10.1, 5.9), 119.7, 111.7 (dd, $J$ = 21.5, 3.6), 104.1 (t, $J$ = 26.2), 62.0, 51.9, 51.0, 50.6, 41.3, 23.7 (3C); $[\alpha]_{405}^{25}$ −161.8 (c 0.1, MeOH). Anal. Calcd for $C_{15}H_{19}F_2NO_2$: C, 63.59; H, 6.76; F, 13.41; N, 4.94. Found: C, 63.50; H, 6.81; F, 13.11; N, 4.91.

**(3*S*,4*R*)-1-*tert*-Butyl-4-(2,4-difluorophenyl)pyrrolidine-3-carboxamide (19*t*).** An analytical sample of the trans amide was prepared from acid **1**, via the acyl imidazole and quenching with ammonium hydroxide: $^1$H NMR ($CDCl_3$) $\delta$ 7.28 (m, 1H), 6.84−6.73 (om, 2H), 6.60 (br s, 1H), 5.92 (br s, 1H), 3.67 (m, 1H), 3.26 (t, $J$ = 8.7, 1H), 3.08 (dd, $J$ = 9.2, 4.2, 1H), 2.98 (t, $J$ = 8.3, 1H), 2.87 (m, 1H), 2.61 (t, $J$ 8.5, 1H), 1.11 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.8, 161.7 (dd, $J$ = 248.4, 12.9), 160.7 (dd, $J$ = 248.6, 12.0), 129.8 (dd, $J$ = 9.4, 6.4), 126.1 (dd, $J$ = 14.1, 3.6), 111.4 (dd, $J$ = 20.9, 3.6), 104.0 (q, $J$ = 51.8), 53.2, 52.4, 51.2, 50.4, 41.5, 26.1 (3C). Anal. Calcd for $C_{15}H_{20}F_2N_2O$: C, 63.81; H, 7.14; N, 9.92; F, 13.46; O 5.67. Found: C, 63.72; H, 7.00; N, 9.89, F, 13.91.

**(1*S*)-2-Chloro-1-phenylethanol (21)**. Prepared from 2-chloro-1-phenylethanone using experimental procedure as described for **5**. The chiral assay (HPLC Condition J) of crude **21** was 99.8% ee (retention time: S-isomer, 13.4 min; R-isomer, 15.0 min). The spectroscopic data are consistent with the literatures.[22]

**(1*S*)-2-(*tert*-Butylamino)-1-phenylethanol (24)**. Prepared from chloro-alcohol **21** using experimental procedure as described for **3**. The chiral assay (HPLC Condition F) of isolated **24** was >99.5% ee (retention time: S-isomer, 4.0 min; R-isomer, 4.7 min). mp (DSC): onset 106.51 °C, end 108.59 °C, peak 107.82 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.24−7.40 (m, 5H), 4.61 (dd, $J$ = 8.8, 3.7, 1H), 2.88 (dd, $J$ = 11.9, 3.7, 1H), 2.62 (dd, $J$ = 11.8, 8.8, 1H), 1.11 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 143.0, 128.3 (2C), 127.4, 125.8 (2C), 72.4, 50.32, 50.27, 29.2 (3C). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.67; H, 10.17; N, 7.20.

**(1*S*)-2-Bromo-1-(4-methoxyphenyl)ethanol (23).**[22] Prepared from 2-bromo-1-(4-methoxyphenyl)-ethanone using experimental procedure as described for **5**, except the substrate was added as a THF solution. The chiral assay (HPLC Condition K) of crude **26** was 91% ee $^1$H NMR ($CDCl_3$) $\delta$ 7.28 (d, $J$ = 8.6, 2H), 6.89 (d, $J$ = 8.7, 2H), 4.84 (m, 1H), 3.80 (s, 3H), 3.45−3.62 (om, 2H), 2.98 (bs, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.4, 132.5, 127.1 (2C), 113.9 (2C), 73.2, 55.1, 38.8.

**(1*S*)-2-(*tert*-Butylamino)-1-(4-methoxyphenyl)ethanol (26).** Prepared from 4′-methoxy-2-bromo acetophenone using experimental procedure as described for **3**. The chiral assay (HPLC Condition F) of isolated **26** was 99% ee (retention time: S-isomer, 5.0 min; R-isomer, 5.7 min). mp (DSC): onset 110.12 °C, end 114.32 °C, peak 112.90 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.30 (d, $J$ = 8.7, 2H), 6.89 (d, $J$ = 8.7, 2H), 4.55 (dd, $J$ = 8.9, 3.6, 1H), 3.81 (s, 3H), 2.85 (dd, $J$ = 11.7, 3.7, 1H), 2.59 (dd, $J$ = 11.7, 8.8, 2H), 1.10 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.0, 135.0, 127.0 (2C), 113.7 (2C), 72.1, 55.3, 50.3, 50.2, 29.2 (3C). Anal. Calcd for $C_{12}H_{19}NO$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.53; H, 9.78; N, 6.11.

**3-{*tert*-Butyl[(2*S*)-2-hydroxy-2-phenylethyl]amino}-propanenitrile (28).** Prepared from amino-alcohol **24** using experimental procedure as described for **8**. The chiral assay (HPLC Condition G) of isolated **28** was >99.5% ee (retention time: S-isomer, 7.2 min; R-isomer, 8.4 min). $^1$H NMR ($CDCl_3$) $\delta$ 7.38 (m, 4H), 7.36 (m, 1H), 4.57 (dd, $J$ = 10.2, 3.7, 1H), 3.70 (bs, −OH), 2.99 (m, 1H), 2.86 (m, 1H), 2.75 (dd, $J$ = 13.9, 3.7, 1H), 2.60−2.40 (m, 3H), 1.15 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 142.4, 128.4, 127.6, 125.8, 118.8, 71.3, 59.7, 55.7, 47.4, 27.3, 20.2; HRMS *m/z* [M + H]$^+$ calcd for $C_{15}H_{23}N_2O$, 247.1810; found, 247.1805.

**3-{*tert*-Butyl[(2S)-2-hydroxy-2-(4-methoxyphenyl)ethyl]-amino}propanenitrile (29).** Prepared from amino-alcohol **26** using experimental procedure as described for **8**. The chiral assay (HPLC Condition G) of isolated **28** was 98% ee (retention time: R-isomer, 9.2 min; S-isomer, 10.2 min). $^1$H NMR ($CDCl_3$) $\delta$ 7.27 (d, $J$ = 8.7, 2H), 6.87 (d, $J$ = 8.7, 2H), 4.50 (dd, $J$ = 10.1, 3.7, 1H), 3.77 (s, 3H), 3.66 (bs, −OH), 2.96 (m, 1H), 2.83 (m, 1H), 2.68 (dd, $J$ = 13.9, 3.7, 1H), 2.55−2.40 (m, 3H), 1.12 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.1, 134.5, 127.0, 118.8, 113.8, 71.0, 59.7, 55.6, 55.2, 47.4, 27.3, 20.2; HRMS *m/z* [M + H]$^+$ calcd for $C_{16}H_{25}N_2O_2$, 277.1916; found, 277.1909.

**(3*S*,4*R*)-1-*tert*-Butyl-4-phenylpyrrolidine-3-carbonitrile (30).** Prepared from alcohol-nitrile **28** using experimental procedure as described for **10**. After workup the crude material was used as is in the next step. $^1$H NMR ($CDCl_3$) $\delta$ 7.37−7.33 (m, 4H), 7.29 (m, 1H), 3.52 (dd, $J$ = 15.8, 8.1, 1H), 3.32 (t, $J$ = 12.2 Hz, 1H), 3.23 (t, $J$ = 9.0, 1H), 3.00−3.10 (m, 2H), 2.91 (t, $J$ = 8.3, 1H), 1.15 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.8, 129.0, 127.6, 127.2, 121.0, 53.3 (2), 50.7, 48.9, 36.1, 25.9; HRMS *m/z* [M+H]$^+$ calcd for $C_{15}H_{20}N_2$, 229.1705; found, 229.1704.

**(3*S*,4*R*)-1-*tert*-Butyl-4-(4-methoxyphenyl)pyrrolidine-3-carbonitrile (31).** Prepared from alcohol-nitrile **29** using experimental procedure as described for **10**. After workup the crude material was used as is in the next step. $^1$H NMR ($CDCl_3$) $\delta$ 7.25 (d, $J$ = 8.7 Hz, 2H), 6.88 (d, $J$ = 8.7 Hz, 2H), 3.81 (s, 3H), 3.46 (dd, $J$ = 15.9, 8.0, 1H), 3.25 (t, $J$ = 8.3, 1H), 3.17 (t, $J$ = 8.8, 1H), 3.01 (t, $J$ = 8.3, 1H), 2.94 (AB q, $J$ = 16.1, 8.0, 1H), 2.81 (AB q, $J$ = 9.2, 7.4, 1H), 1.12 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.1, 133.3, 128.3, 121.5, 114.4, 55.5, 53.6, 52.7, 50.8, 48.4, 36.5, 26.1; HRMS *m/ z* [M+H]$^+$ calcd for $C_{16}H_{23}N_2O$, 259.1810; found, 259.1803.

**(3*S*,4*R*)-1-*tert*-Butyl-4-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid (33).** Prepared from pyrrolidine-nitrile **31** using experimental procedure as described for **1**. The chiral assays (HPLC Condition H) of crude and isolated **33** were 95% ee and >99% ee respectively (retention time: 3S,4R-isomer, 18.8 min; 3R,4S-isomer, 19.4 min). $^1$H NMR ($CD_3OD$) $\delta$ 7.31 (d, $J$ = 8.7, 2H), 6.88 (d, $J$ = 8.7, 2H), 4.89 (OH), 3.79−3.68 (om, 3H), 3.76 (s, 3H), 3.55 (br t, $J$ = 10.6, 1H), 3.25 (br t, $J$ = 11.2, 1H), 3.11 (AB q, $J$ = 18.8, 10.0, 1H), 1.41 (s, 9H); $^{13}$C

NMR ($CD_3OD$) $\delta$ 177.2, 160.7, 131.3, 129.9, 115.4, 62.6, 55.9, 55.2, 54.1, 53.3, 48.5, 25.0. HRMS *m/z* $[M + H]^+$ calcd for $C_{16}H_{24}NO_3$, 278.1756; found, 278.1754.

**(3*S*,4*R*)-1-*tert*-Butyl-4-phenylpyrrolidine-3-carboxylic acid (32).** Prepared from pyrrolidine-nitrile **30** using experimental procedure as described for **1**. The chiral assays (HPLC Condition I) of crude and isolated **33** were 94% ee and 99% ee respectively (retention time: 3S,4R-isomer, 21.4 min; 3R,4S-isomer, 23.4 min). $^1H$ NMR ($CD_3OD$) $\delta$ 7.40 (m, 2H), 7.34 (m, 2H), 7.26 (m, 1H), 3.85 (m, 1H), 3.80−3.70 (m, 2H), 3.58 (br t, $J$ = 10.5, 1H), 3.31 (m, 1H), 3.16 (AB q, $J$ = 18.8, 9.6, 1H), 1.43 (s, 9H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 175.5, 138.0, 128.4, 127.3, 127.2, 61.1, 53.7, 52.3, 51.9, 47.4, 23.5. HRMS *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$, 248.1651; found, 248.1649.

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**Supporting Information Available:** General experimental methods and copies of $^1H$ and $^{13}C$ NMR for compounds **6**, **9**, **23**, and **28**−**33**. This material is available free of charge via the Internet at http:// pubs.acs.org.

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